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Course of arterial hypertension during breast cancer chemotherapy with anthracyclines

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ABSTRACT

Aim. To study the characteristics of the course of arterial hypertension (AH) and subclinical cardiac damage during breast cancer chemotherapy with doxorubicin.

Materials and methods. The study included a total of 27 women with breast cancer (BC) and a history of controlled hypertension who were to receive chemotherapy with anthracyclines. Twelve women had stage 1 hypertension; 15 women had stage 2 hypertension. The patients received dual antihypertensive therapy according to clinical guidelines. All patients underwent echocardiography and 24-hour blood pressure monitoring at baseline, after the last course of chemotherapy, and 12 months after the end of chemotherapy. The control group included 35 women with BC without a history of AH, who also were to receive anthracycline chemotherapy.

Results. A significant relationship between pre-existing AH and the development of left ventricular systolic dysfunction 12 months after the completion of chemotherapy ($p = 0.01$) was found. According to 24-hour blood pressure monitoring, 15 women (55.6%) showed deterioration of blood pressure control after the completion of chemotherapy, which required modification of antihypertensive therapy by adding one more drug to the treatment regimen. At 12 months after the end of chemotherapy, in 13 women, hypertension control was reached with triple antihypertensive therapy. In two women, hypertension became resistant, which required prescription of a four-component antihypertensive regimen.

Conclusion. Pre-existing AH plays an essential role in the development of anthracycline-induced cardiotoxicity, despite the quality of blood pressure control. Polychemotherapy with anthracyclines may deteriorate blood pressure control in patients with AH, which requires addition of antihypertensive drugs to the treatment regimen.

Keywords: arterial hypertension, chemotherapy, anthracyclines, heart failure, cardio-oncology

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Conformity with the principles of ethics. All patients signed an informed consent to participate in the study. The study was approved by the local Ethics Committee at City Clinical Hospital No. 16 (Protocol No. 245 of 25.11.2020).

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Течение артериальной гипертензии на фоне химиотерапии рака молочной железы антрациклинами

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РЕЗЮМЕ

Цель. Изучение особенностей течения артериальной гипертензии (АГ) и развития субклинического поражения сердца на фоне химиотерапии доксорубицином рака молочной железы (РМЖ).

Материалы и методы. В исследование включены 27 женщин с РМЖ, имеющих в анамнезе контролируемую АГ, которым планировалась полихимиотерапия (ПХТ) с использованием антрациклиновых антибиотиков. У 12 женщин зарегистрирована гипертоническая болезнь 1-й стадии, у 15 женщин – 2-й стадии. Пациентки получали двойную антигипертензивную терапию согласно клиническим рекомендациям. Всем пациенткам проводились эхокардиография и суточное мониторирование артериального давления (АД) исходно, после последнего курса и через 12 мес после окончания ПХТ. В группу контроля включены 35 женщин с РМЖ без АГ анамнезе, которым также планировалась терапия антрациклинами.

Результаты. Наблюдалась значимая взаимосвязь между ранее существовавшей АГ и развитием систолической дисфункцией левого желудочка через 12 мес после завершения химиотерапии ($p = 0,01$). По данным суточного мониторирования АД, у 15 женщин (55,6%) зарегистрировано ухудшение контроля АД после окончания ПХТ, что потребовало модификации антигипертензивной терапии путем добавления в схему лечения дополнительного препарата. Через 12 мес после окончания ПХТ у 13 женщин АГ имела контролируемый характер течения, что было достигнуто тройной антигипертензивной терапией; у двух женщин АГ приобрела резистентный характер течения, что потребовало назначения четырехкомпонентной схемы гипотензивной терапии.

Заключение. Ранее существовавшая АГ играет очень важную роль в развитии кардиотоксичности, вызванной химиотерапией на основе антрациклинов, несмотря на качество контроля АД. Полихимиотерапия антрациклинами может ухудшать контроль АД у больных с АГ, что сопровождается необходимостью добавления дополнительных антигипертензивных препаратов.

Ключевые слова: артериальная гипертензия, химиотерапия, антрациклины, сердечная недостаточность, кардиоонкология

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

Соответствие принципам этики. Все пациенты подписали информированное согласие на участие в исследовании. Исследование одобрено локальным этическим комитетом ГБУЗ «Городская клиническая поликлиника № 16» (протокол № 245 от 25.11.2020).

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INTRODUCTION

Arterial hypertension (AH) is one of the most common diseases in the general population. Its prevalence reaches up to 30-45% and increases with age [1]. Cancer is also a common pathology, which is the second leading cause of death worldwide [2]. The average age of population is increasing, and cancer patients have longer overall survival due to improved anticancer therapy [2]. In addition, some risk factors associated with the development of AH, such as obesity, type 2 diabetes mellitus, smoking, and sedentary lifestyle, are also associated with the development of malignant neoplasms [3]. Therefore, it is not surprising that an increasing number of cancer patients seek medical care with a history of AH. In a review by M. Jain et al., the incidence of AH in cancer patients reached 37%, making it the most common concomitant cardiovascular disease reported in patients with malignant neoplasms [4]. On the other hand, AH is also a common complication in cancer patients which develops during certain types of chemotherapy [5, 6].

Childhood Cancer Survivor Study, which compared more than 10,000 adult survivors of childhood cancer with 3,000 siblings, showed that patients with a history of cancer were more likely to have AH than the general population. The researchers found that the prevalence of AH was 40% versus 25% at the age of 45 years, respectively [7]. AH may increase the risk of chemotherapy-induced cardiotoxicity and, if poorly controlled, can lead to discontinuation of treatment for the malignancy [5, 6]. AH can develop in patients receiving various types of chemotherapy following direct effects or an indirect effect through mechanisms associated with nephrotoxicity [8].

The main anticancer drugs which effect may be complicated by AH are vascular endothelial growth factor (VEGF) inhibitors and tyrosine kinase inhibitors (TKIs). A recent meta-analysis assessed the risk of cardiovascular disease during TKI therapy compared to standard chemotherapy. Seventy-one randomized controlled trials involving more than 29,000 patients were included in the review. The results showed that the relative risk of developing AH during TKI therapy was 3.78 (95% confidence interval (CI) 3.15–4.54) compared to the age- and comorbidity-matched controls [9]. AH was reported in 50% of patients receiving anti-VEGF therapy [10]. In the meantime, there are practically no studies on the effect of anthracyclines on the course of AH which was manifested before the initiation of cancer chemotherapy.

The aim of the study was to investigate the characteristics of the course of AH during breast cancer chemotherapy with doxorubicin.

MATERIALS AND METHODS

The protocol for the 12-month prospective study included patients who signed an informed consent to participate in the study. The study was approved by the local Ethics Committee at City Clinical Hospital No. 16 (Protocol No. 245 of 25.11.2020).

Inclusion criteria: 1) women aged 40–60 years with BC; 2) use of AC (doxorubicin + cyclophosphamide) or TAC (doxorubicin + cyclophosphamide + docetaxel) chemotherapy regimens; 3) complete remission for BC within 12 months after the end of polychemotherapy (PCT); 4) controlled stage 1–2 hypertension.

Exclusion criteria: 1) confirmed cardiovascular pathology before the initiation of chemotherapy, except for hypertension (heart valve disease, cardiomyopathy, chronic heart failure, history of primary pulmonary hypertension); 2) the use of targeted therapy drugs and aromatase inhibitors for

the treatment of BC; 3) relapse of BC or emergence of new cancer during the follow-up; 4) type 1 and 2 diabetes mellitus; 5) concomitant severe renal, hepatic or multiple organ failure; 6) indications of poor drug tolerance; 7) anemia; 8) chronic alcoholism, mental disorders.

The patients were followed up at three stages: before the initiation of anthracycline therapy, after the last course of PCT, and 12 months after the completion of BC therapy. At the indicated observation points, echocardiography (echo) and 24-hour BP monitoring were performed. During echo, linear and volumetric heart chamber dimensions were assessed; left ventricular ejection fraction (LVEF) was calculated by the Simpson method, and the thickness of the walls of the left and right ventricles was measured. Left ventricular myocardial mass (LVMM) and left ventricular mass index (LVMI) were determined from M-mode measurements in accordance with the recommendations of the American Society of Echocardiography (ASE). Given prevalence among the examined individuals with excess body weight, LVMI was calculated using the formula LVMM / height$^{2.7}$. Global longitudinal strain (GLS) of the LV was studied by two-dimensional speckle tracking echocardiography.

The characteristics of the course of AH were assessed in 27 women with BC during chemotherapy and for 12 months after its completion. We also assessed initial signs of asymptomatic myocardial dysfunction according to cardiotoxicity criteria after BC chemotherapy with anthracyclines proposed by the European Society of Cardiology in 2022 [6]: LVEF ≥ 50% and a decrease in left ventricular GLS by more than 15% from the baseline value.

The control group included 35 women with BC without a history of AH, who also received BC therapy using AC or TAC regimens. In this group, the development of AH and other cardiovascular diseases, including anthracycline-induced cardiac dysfunction, was assessed within 12 months after the end of PCT.

Statistical processing of the results was carried out using the STATISTICA 13.3 software package (StatSoft, Inc., USA). Quantitative variables were presented as the median and the interquartile range Me (Q_{25}; Q_{75}). To compare two independent samples, the Mann – Whitney test was used. The critical significance level p for all statistical procedures was taken equal to 0.05.

RESULTS

Prior to PCT, the studied groups of women with BC were comparable in age, body mass index, and LVEF (Table 1).

Table 1

Baseline characteristics of patients depending on the presence of AH

Parameter	Patients with AH, n = 27	Patients without AH, n = 35	p
Age, years, *Me* (Q_{25}; Q_{75})	51 (48; 56)	50 (46; 53)	0.318
Body mass index, kg / m^2, *Me* (Q_{25}; Q_{75})	25.2 (23.6; 26.9)	24.8 (23.1; 26.3)	0.183
Cumulative dose of doxorubicin, mg / m^2, *Me* (Q_{25}; Q_{75})	360 (300; 360)	360 (300; 360)	0.893
Chemotherapy regimen, *n* (%): – AC; – TAC	 15 (55.6) 12 (44.4)	 20 (57.1) 15 (42.9)	 0.729 0.773
Left-sided radiation therapy, *n* (%)	9 (33.3)	11 (31.4)	0.851
Stage of hypertension, *n* (%): – stage 1; – stage 2	 12 (44.4) 15 (55.6)	 – –	 – –
Heart rate, *Me* (Q_{25}; Q_{75})	72 (66; 77)	76 (68; 82)	0.095
Systolic BP, mm Hg., *Me* (Q_{25}; Q_{75})	125 (120; 130)	115 (110; 120)	0.031
Diastolic BP, mm Hg., *Me* (Q_{25}; Q_{75})	75 (70; 80)	70 (70; 80)	0.062
LVEF, %, *Me* (Q_{25}; Q_{75})	63 (59; 66)	61.0 (58; 64)	0.261
GLS, %, *Me* (Q_{25}; Q_{75})	–19.3 (–17.8; 20.5)	–19.6 (–18.0; 20.7)	0.692
LVMI, g / m^2, *Me* (Q_{25}; Q_{75})	109.4 (89.3; 126.4)	85.2 (75.1; 92.8)	<0.001

Table 1 (continued)

Parameter	Patients with AH, *n* = 27	Patients without AH, *n* = 35	*p*
Antihypertensive therapy, *n* (%):			
– ACE inhibitors;	16 (59.3)	–	–
– ARBs;	11 (40.7)	–	–
– DCCBs;	17 (63.0)	–	–
– diuretics;	7 (25.9)	–	–
– β-adrenergic blockers	3 (11.1)	–	–

Note. Here and in Table 2: AH – arterial hypertension, AC – polychemotherapy regimen (doxorubicin + cyclophosphamide), TAC – polychemotherapy regimen (doxorubicin + cyclophosphamide + docetaxel), LVEF – left ventricular ejection fraction, BP – blood pressure, LVMI – left ventricular mass index, ACE – angiotensin-converting enzyme, ARB – angiotensin receptor blocker, DCCB – dihydropyridine calcium channel blocker, GLS – global longitudinal strain. *p* – probability of type I error.

In patients with AH, a significantly increased LVMI was registered ($p < 0.001$) compared to the control group. The cumulative dose of doxorubicin and the applied PCT regimens were comparable in the groups. Before the initiation of PCT, stage 1 hypertension was registered in 12 women, and stage 2 hypertension – in 15 women with AH.

A significant correlation was revealed between pre-existing AH and the development of left ventricular systolic dysfunction 12 months after the completion of chemotherapy ($p = 0.01$) (Table 2): according to the criteria of the European Society of Cardiology [6], signs of anthracycline-induced cardiotoxicity were recorded in 6 (22.2 %) women with AH and in 2 (5.7%) patients in the control group.

In 15 women (55.6%) with AH, deterioration of blood pressure control was recorded after completion of PCT, which required modification of antihypertensive therapy by adding one more drug to the treatment regimen. In the control group, two people developed stage 1 hypertension within 12 months after the completion of PCT, the control of which was not achieved by lifestyle modification and required prescription of two antihypertensive drugs. In women with AH after the completion of PCT, a non-significant increase in LVMI was noted.

At 12 months after the end of chemotherapy, in 13 women, hypertension control was reached with triple antihypertensive therapy. In two women, hypertension became resistant, which required prescription of a four-component antihypertensive regimen with the addition of mineralocorticoid receptor antagonists (Figure).

Table 2

Changes in the main clinical and echocardiography parameters in the study groups

Parameter	At baseline	After the end of PCT	Twelve months after the end of PCT	*p*
Patients with AH, n = 27				
Stage of hypertension, *n* (%):				
– stage 1;	12 (44.4)	12 (44.4)	10 (37.0)	0.416
– stage 2	15 (55.6)	15 (55.6)	17 (63.0)	0.416
Heart rate, *Me* (Q_{25}; Q_{75})	72 (66; 77)	76 (71; 80)	70 (65; 74)	0.272
Systolic BP, mm Hg., *Me* (Q_{25}; Q_{75})	125 (120; 130)	130 (120; 135)	125 (120; 130)	0.612
Diastolic BP, mm Hg., *Me* (Q_{25}; Q_{75})	75 (70; 80)	80 (75; 85)	75 (70; 80)	0.749
LVEF, %, *Me* (Q_{25}; Q_{75})	63 (59; 66)	62 (58; 66)	59 (55; 62)	0.083
GLS, %, *Me* (Q_{25}; Q_{75})	–19.3 (–17.8; 20.5)	–18.2 (–16.9; 19.8)	–18.0 (–16.8; 19.4)	0.174
Development of anthracycline-induced cardiac dysfunction, *n* (%)	–	–	6 (22.2)	–
LVMI, g / m^2, *Me* (Q_{25}; Q_{75})	109.4 (89.3; 166.4)	107.8 (91.2; 127.5)	114.3 (90.1; 132.6)	0.153
Antihypertensive therapy, *n* (%):				
– ACE inhibitors;	16 (59.3)	16 (59.3)	16 (59.3)	1.0
– ARBs;	11 (40.7)	11 (40.7)	11 (40.7)	1.0
– DCCBs;	17 (63.0)	27 (100.0)	27 (100.0)	0.023
– diuretics;	7 (25.9)	9 (33.3)	7 (25.9)	1.0
– β-adrenergic blockers;	3 (11.1)	6 (22.2)	8 (29.6)	0.041
– MCRAs	–	–	2 (7.4)	0.932

Table 2 (continued)

Parameter	At baseline	After the end of PC	Twelve months after the end of PCT	*p*
Patients without AH, n = 35				
Stage of hypertension, *n* (%): – stage 1; – stage 2	 – –	 – –	 2 (5.7) –	 – –
Heart rate, *Me* (Q_{25}; Q_{75})	76 (68; 82)	81 (75; 88)		
Systolic BP, mm Hg., *Me* (Q_{25}; Q_{75})	115 (110; 120)	115 (110; 120)	115 (110; 120)	0.621
Diastolic BP, mm Hg., *Me* (Q_{25}; Q_{75})	70 (70; 80)	70 (70; 80)	70 (70; 80)	0.811
LVEF, %, *Me* (Q_{25}; Q_{75})	61.0 (58; 64)	60,0 (57; 64)	59 (57; 62)	0.354
GLS, %, *Me* (Q_{25}; Q_{75})	–19.6 (–18.0; 20.7)	–18.7 (–17.5; 20.1)	–19.2 (–17.9; 20.5)	0.452
Development of anthracycline-induced cardiac dysfunction, *n* (%)	–	–	2 (5.7)*	–
LVMI, g / m^2, *Me* (Q_{25}; Q_{75})	85.2 (75.1; 92.8)	86.4 (74.2; 93.8)	87.1 (75.4; 93.1)	0.632
Parameter	At baseline	Afte the end of PCT	Twelve months after the end of PCT	*p*
Antihypertensive therapy, *n* (%): – ACE inhibitors; – ARBs; – DCCBs; – diuretics; – β-adrenergic blockers; – MCRAs	 – – – – – –	 – – – – – –	 2 (5.7) - - - 2 (5.7) –	 – – – – – –

*p = 0.01 compared to the AH group.

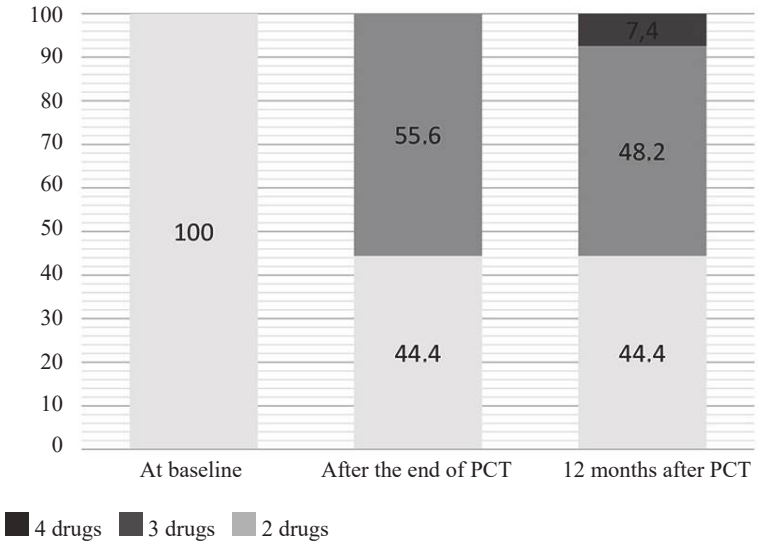

Figure. Number of antihypertensive drugs in the groups of patients with AH, %

DISCUSSION

Anthracyclines have broad antitumor activity. They are highly effective and are among the most frequently prescribed drugs for the treatment of malignant neoplasms. However, their clinical use is limited due to excessive generation of reactive oxygen species (ROS) and the development of cardiotoxicity with progression to heart failure [5, 6]. It was proven that the presence of cardiovascular diseases, including AH, is a risk factor for the development of myocardial dysfunction [5, 6].

This phenomenon was confirmed in our study: the development of anthracycline-induced cardiotoxicity 12 months after the end of PCT was more often (p = 0.01) registered in women with AH than in the control group. In the meantime, there are practically no studies on the effect of anthracyclines on the course of AH manifested before the initiation of antitumor chemotherapy. In our work, 55.6% of patients with

AH showed deterioration of blood pressure control after completion of PCT. The effect of anthracyclines on BP may be due to the development of endothelial dysfunction and activation of the renin – angiotensin – aldosterone system (RAAS) and sympathoadrenal system during and after the use of anthracyclines, which is confirmed in a number of experimental studies and clinical trials.

Recently increasing attention has been paid to anthracycline-induced endotheliotoxicity [11]. Many studies have confirmed that anthracycline-induced endotheliotoxicity, as well as cardiotoxicity and nephrotoxicity, drastically limits their clinical use [5, 6, 11]. Therefore, doxorubicin can cause severe damage to the vascular endothelium. Excessive generation of ROS is known to cause subsequent development of anthracycline-induced cytotoxicity [12], which can lead to endothelial dysfunction, affecting the course of AH.

According to M.M. Said-Ahmed et al., administration of cumulative doses of doxorubicin at a dose of 10, 15, and 20 mg / kg for two weeks resulted in a dose-dependent increase in plasma endothelin-1 (ET-1) levels by 85, 76, and 97%, respectively. In the meantime, the level of nitric oxide (NO) in the blood plasma did not change, while the production of NO in the myocardium significantly increased [13]. A recent study demonstrated a decrease in the effectiveness of NO-dependent mechanisms regulating vascular tone during a single dose of chemotherapy at 4 mg / kg [14]. On the other hand, a number of studies have demonstrated an increase in NO production, which is associated with upregulation of the inducible NO synthase (*iNOS*) and endothelial NO synthase (*eNOS*) genes [15, 16]. High concentrations of NO produced by the iNOS or eNOS enzymes stimulate generation of peroxynitrite following a reaction with superoxide anion. The resulting peroxynitrite leads to lipid peroxidation [17], which can result in damage to endothelial cells.

Studies examining the ET-1 / NO axis found low eNOS activity in the presence of severe endothelial damage, which may lead to increased ET-1 levels [18]. J. Yamashita et al. showed that monitoring plasma ET-1 levels can help detect subclinical cardiotoxicity of doxorubicin [19]. Excessive levels of intracellular calcium, which are caused by anthracyclines, are known to contribute to mitochondrial dysfunction, high-energy phosphate depletion, increased muscle stiffness, impaired contractile function, and cell death. ET-1 can induce the production of inositol phosphates, which increase intracellular Ca^{2+} levels by releasing it from intracellular stores. This process results in calcium overload of endothelial cells [20].

To date, the influence of anthracyclines on the activity of the RAAS, which is a complex hormone system crucial for both normal functioning of the cardiovascular system and regulation of the fluid and electrolyte balance of the body, has been proven. An imbalance in the RAAS leads to diseases, such as AH, heart failure, and even cancer [21]. Available data make it clear that increased angiotensin II (ATII) activity is one of the key events in anthracycline-induced endothelial dysfunction. The significant effect of ATII may be due to its increased synthesis or enhanced signaling from receptors.

M. Zheng et al. noted a three-fold increase in the level of ATII in the blood plasma of animals treated with doxorubicin compared to the controls [22]. High levels of ATII were also found in the myocardium and paraventricular nucleus of the hypothalamus (one of the centers regulating the cardiovascular system) [23]. These results indicate that under the influence of anthracyclines, ATII affects not only the heart and blood vessels, but also central control of the cardiovascular system. The ability of anthracyclines to induce excitation of the sympathetic nervous system at the central level has been proven [24].

In addition, it has been shown that under the influence of anthracyclines, renin activity increases, stimulating greater conversion of angiotensinogen to angiotensin I (ATI) [25]. A significant increase in ATI levels after doxorubicin administration may be an indirect sign of increased renin activity. At the same time, aliskiren, which is a renin inhibitor, caused a decrease in the concentration of ATI [25].

Another mechanism is associated with increased activity of angiotensin-converting enzyme (ACE). Long-term treatment with doxorubicin led to a significant, almost 2.3-fold increase in ACE activity in the heart of hamsters compared to control animals [26].

ATII exerts its effects through angiotensin type 1 (AT1R) and angiotensin type 2 receptors (AT2R). However, AT1R appears to play a key role in the development of anthracycline-induced endothelial dysfunction. It was shown that doxorubicin stimulated AT1R mRNA expression with an increasing drug

dose in cardiomyocytes [27]. In contrast to AT1R, AT2R, which mediates the protective effects of ATII, is inhibited by doxorubicin [28].

Therefore, we can conclude that the use of anthracyclines results in an imbalance of the main RAAS axes, namely hyperactivation of the angiotensinogen / ATII / AT1R axis. Consequently, the interference of doxorubicin in the secretion of essential endothelial factors and the RAAS, which play a crucial role in the functioning of the cardiovascular system, leads to a decrease in its adaptability. There is now growing evidence that anthracyclines may directly increase the risk of developing AH. Potential mechanisms include decreased capillary density, impaired neovascularization, and histologic changes in the vasculature, including intimal hyperplasia, luminal stenosis, and loss of smooth muscle cells [29]. In addition, vasomotor dysfunction resulting from decreased eNOS activity leads to decreased NO generation by endothelial cells, potentially contributing to the development of AH [30–32].

Antihypertensive therapy for AH in patients receiving chemotherapy has some distinctive features. In our study, 12 months after the end of PCT in 13 women, hypertension control was reached with triple antihypertensive therapy. In two women, AH became resistant, which required the prescription of a four-component antihypertensive regimen.

Changes in lifestyle and reduced sodium intake are recommended, regardless of anticancer therapy used, as they have a BP-lowering effect in many patients. However, strict adherence to recommendations for non-pharmacological BP control is challenging for many patients [33].

The choice of antihypertensive drugs in cancer patients is influenced by several factors. For example, the use of hydrochlorothiazide (HCTZ) was associated with the development of nonmelanoma skin cancer in two large studies performed in Denmark [34] and in the UK [35]. Researchers of the latter found an association between the use of HCTZ and the risk of developing basal and squamous cell skin cancer. On the other hand, studies conducted in Taiwan [36] and Korea [37] showed no association of HCTZ application with the development of skin cancer. However, the use of thiazide-like diuretics, such as chlorthalidone and indapamide, was not associated with an increased risk of skin cancer; therefore, some experts recommend the use of these drugs rather than HCTZ for the treatment of hypertension [38].

Several studies suggested that use of ACE inhibitors (ACEIs) may be associated with an increased risk of lung cancer. However, these studies were heavily criticized due to various limitations in data collection and interpretation, leading to the conclusion that there is currently insufficient evidence for altering clinical practice [39]. The European Society of Cardiology recommends angiotensin receptor blockers (ARBs) and dihydropyridine calcium channel blockers (DCCBs) as first-line therapy for AH. With the development of resistant hypertension, it is recommended to add β-adrenergic blockers, spironolactone, and NO donors, such as isosorbide mono/dinitrate or hydralazine, to therapy [6].

Regardless of the type of a drug used, more than one drug is required to treat AH caused by anticancer therapy. J.B. Cohen et al. suggested that patients with BP above the target values should start receiving DCCB in the absence of proteinuria and ACEI / ARB in the presence of proteinuria, titrated to an effective dose. The next step in BP management should be adding a drug from the class that was not initially prescribed (i.e. ACEI / ARB if CCB was received first, and vice versa). The third step in treatment intensification should be the use of a diuretic, unless contraindicated, followed by a MCRA or a β-adrenergic blocker [3].

Thus, AH is a common comorbidity as well as an adverse event in cancer patients and should, therefore, be closely monitored. The effect of antitumor therapy on the development of AH and treatment effectiveness should be thoroughly studied, since the prevention of cardiovascular morbidity and mortality is of paramount importance both in active cancer patients and in people with a history of cancer.

CONCLUSION

Pre-existing AH plays a crucial role in the development of anthracycline-induced cardiotoxicity, despite the quality of BP control. PCT with anthracyclines may deteriorate BP control in patients with AH, which requires addition of new antihypertensive drugs to the treatment regimen.

Despite efforts made to understand the role of various antineoplastic agents in increasing the risk of AH and influencing its course, many mechanisms

have not been fully defined, and clinical studies assessing the effectiveness and safety of specific antihypertensive drugs in cancer survivors are limited. Survivor populations are heterogeneous and have rich treatment history; therefore, the diagnosis and treatment of AH may need to be tailored to different subgroups. Understanding the mechanisms responsible for changes in BP in cancer patients will facilitate identification of new therapeutic targets in patients with AH.

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Berezikova E.N., Shilov S.N. – conception and design, analysis and interpretation of the data, drafting of the manuscript. Popova A.A., Grakova E.V. – conception and design, justification of the manuscript. Neupokoeva M.N., Kopeva K.V., Yushin A.Ju. – analysis and interpretation of the data. Teplyakov A.T., Kalyuzhin V.V. – final approval of the manuscript for publication.

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